

Remarks

Claims 2, 8, and 11 remain in this application. Claims 1, 9, and 10 have been cancelled. Claims 2 and 8 have been amended. Claim 2 has been substantially amended to comply with the restriction requirement and to address rejections raised by the Examiner. Basis for the amendment to variable R² is found at page 21, line 11 of the specification. New Claim 2 has been entered to comply with the restriction requirement. Basis for the amendment to Claim 8 may be found at page 21, line 11 of the specification.

Restrictions/Election of Species

The Examiner has required restriction of the invention as originally claimed. Applicants have amended Claim 2 to substantially comply with the election of Group I as presented by the Examiner. Applicants wish to point out that R² has been expanded from benzyl in Group I to benzyl optionally mono- or disubstituted with fluoro. Applicants assert that this modification of the proposed Group I represents a single inventive concept, and places no undue burden on the Examiner for searching or examination. Furthermore, both the species elected by Applicant as well as the species selected by the Examiner fall within this modified Group I, but not within the Group I articulated by the Examiner. Applicants affirm the election of the species of Example 33. This elected species falls within the scope of Claims 2, 8, and 11. Claim 11 has been conformed to the scope of Claim 2

Claim Rejections - 35 U.S.C. § 112, First Paragraph

The examiner has rejected Claims 1, 2, 8, and 9 as failing to comply with the enablement requirement set forth in 35 U.S.C. § 112, first paragraph. The Examiner asserts that these claims are not enabled because “the specification, *while being enabling for substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III, wherein R¹ = -(C₃-C₇cycloalkyl)₀₋₁(C₁-C₆alkyl)*, -pyridyl, -phenyl or -biphenyl, does not reasonably provide enablement for substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III, where R¹ = -(C₃-C₇cycloalkyl)₀₋₁(C₂-C₆alkenyl), -(C₃-C₇cycloalkyl)₀₋₁(C₂-C₆alkynyl), -C₃-C₇cycloalkyl and -H.” Office Action dated August 20, 2008, p. 9.

Claims 1 and 9 have been cancelled. Applicants assert that Claims 2 and 8 meet the requirements of 35 U.S.C. § 112, first paragraph. Applicants have elected Group I of the restriction requirement. As such, R¹ = -(C₃-C₇cycloalkyl)₀₋₁(C₁-C₆alkyl) for which the specification has been deemed enabling by the Examiner. *Id.* Additional basis is provided by Example 32 on page 159 and Examples 33 through 43 on page 160. Further, Applicants

respectfully request R⁶ to be R³⁴ or -CH₂C(O)R³⁵. Basis for the amendment can be found on page 22, lines 14-16.

Since the presently elected scope of the application is now more narrowly drawn around the exemplified compounds of the application, Applicants assert that Claims 2 and 8 meet the requirements of 35 U.S.C. § 112, first paragraph and respectfully request withdrawal of the rejection and allowance of Claims 2 and 8.

Claim Rejections - 35 U.S.C. § 102

The Examiner has rejected Claims 1, 2, 8, and 9 under 35 U.S.C. § 102(e) as being anticipated by WO 05/016876. Claims 1 and 9 have been cancelled. Applicants assert that Claims 2 and 8 are not anticipated by WO 05/016876 under 35 U.S.C. § 102.

In order for a reference to anticipate a claim, it must show each and every feature of the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303, 313 (Fed. Cir. 1983). The reference must disclose each element of the claimed invention “arranged as in the claim.” *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 221 USPQ 481, 485 (Fed. Cir. 1984). The identical invention must be shown in as complete detail as is contained in the . . . claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Note also MPEP §2131.

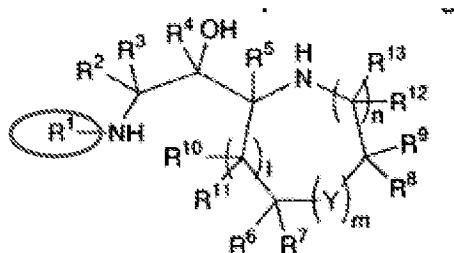


Figure (1)

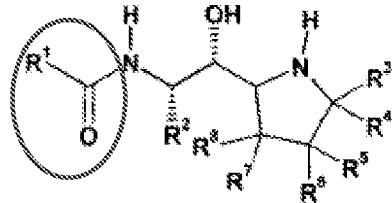


Figure (2)

The genus of WO 05/016876, represented by Figure (1) above, does not contain the moiety, R¹ = -(C₃-C₇cycloalkyl)₀₋₁(C₁-C₆alkyl) as in the present invention, represented by Figure (2) above. In WO 05/016876, R¹ is a carbonyl substituted with the aryl groups, phenyl and pyridinyl. Thus, the R¹ group of WO 05/016876 can neither be a carbonyl substituted with an alkyl group nor a carbonyl substituted with an (cycloalkyl)(alkyl) group.

Therefore, because WO 05/016876 fails to teach each and every feature of the present claims, Applicants assert that the present anticipation rejection is improper and respectfully request allowance of Claims 1, 2, and 8.

Claim Rejections - 35 U.S.C. § 103

The Examiner has rejected Claims 1, 2, 8, and 9 under 35 U.S.C. § 103 as being unpatentable over WO 05/016876 in view of McCarty, et al. in *J. Med. Chem.* 13(5), **1970**, pp. 814-819. Claims 1 and 9 have been cancelled. Applicants assert that Claims 2 and 8 are not obvious in light of WO 05/016876 in view of McCarty, et al.

In order to determine whether an invention is obvious under 35 U.S.C. § 103, it is necessary to: (1) determine the scope and the contents of the prior art; (2) determine the differences between the prior art and the claims at issue; and (3) resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1 (1966). “[I]n cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound.” *Takeda Chemical Industries Ltd. V. Alphapharm Pty, Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). Further, the proposed modification of the prior art must demonstrate a reasonable expectation of success as determined from the vantage point of the skilled artisan at the time the invention was made and the prior art reference or combination of references must teach or suggest all the limitations of the claims. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

Claim 1 of the present application encompasses compounds of the following formula:

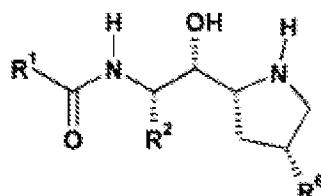


Figure (3)

WO 05/016876 exemplifies the following species relied upon by the Examiner:

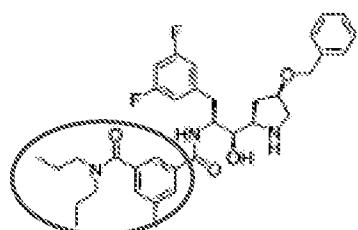


Figure (4)

McCarty, et. al. discloses acyclic amides, such as:

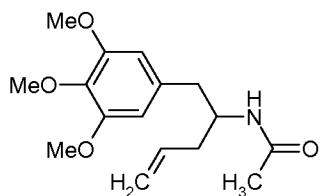


Figure (5)

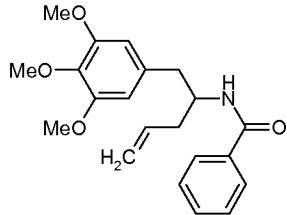


Figure (6)

relied upon by the Examiner which includes a methyl amide as part of the structure, as shown in Figure (5) above, or a benzamide, as shown in Figure (6) above.

To arrive at the compounds within the present application, the prior art must motivate the skilled artisan to both select the above compound, Figure (4), from WO 05/016876 as a starting point for modification and then suggest the modification: to replace the substituted aryl moiety, shown circled in red in Figure (4) above, and replace it with -(C₃-C₇cycloalkyl)₀₋₁(C₁-C₆alkyl), for example a methyl, as in Figure (5) below relied upon by the Examiner.

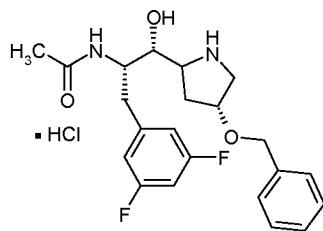


Figure (5)

As a threshold matter, the Examiner has not stated why the skilled artisan would select the species of WO 05/016876, represented by Figure (4) above, as a starting point for modification. This failure alone is sufficient to defeat a finding of *prima facie* obviousness.

Further, the examiner states that “McCarty teaches the alternative utility of acetamides and benzamides . . . wherein a finite number of identified, predictable solutions (i.e., alkyl amides and aryl amides) are presented and explored” creating a claimed combination of elements that would be obvious to try and obvious under 35 U.S.C. § 103. Office Action dated August 20, 2008, p. 18. “[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 1741 (2007). “[I]nventions in most, if not all instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.” *Id.* The field of synthetic organic chemistry is an unpredictable art. Office Action dated August 20, 2008, p. 11 quoting *In re Marzocchi an*

Horton, 169 USPQ at 367 paragraph 3.

Due to the unpredictability of the art, replacing an aryl substituent on a molecule with either an alkyl substituent or a saturated cycloalkyl-alkyl will not lead a skilled artisan to expect a “predictable” result or an expectation of success. The data from McCarty shows that molecules that contain an alkyl-amide or substituted alkyl-amide possess hypotensive activity as compared to molecules that contain an aryl-amide or substituted aryl-amide which do not possess hypotensive activity. *McCarty, et. al.*, p. 815. As such, McCarty actually teaches that alkyl-amides and aryl-amides are not equivalent with respect to pharmacological activities and, therefore, McCarty teaches away from the compounds of the present invention. “The mere fact that it is *possible* to find two isolated disclosures which might be combined in such a way to produce a new compound does not necessarily render such production obvious unless the art also contains something to suggest the desirability of the proposed combination.” *In re Grabiak*, 769 F.2d 729, 732 (Fed.Cir. 1985).

There is no suggestion or incentive that would have motivated the skilled artisan to combine the two references, WO 05/016876 and McCarty, et. al. WO 05/016876 discloses a broad genus, encompassing millions of compounds, and *only* teaching compounds where R¹ is a carbonyl substituted with the aryl groups, phenyl and pyridinyl. Although McCarty, et. al. teaches methyl amides and benzamides, it presents data demonstrating that they are not substitutable for each other. As such, there is no suggestion, incentive, or motivation for the skilled artisan to combine the two references to modify the aryl groups of WO 05/016876 in favor of an alkyl group or saturated cycloalkyl-alkyl group as described in the instant case. Therefore, Applicants assert that a *prima facie* case of obviousness has not been established. Applicants respectfully request withdrawal of the rejection and allowance of the claims.

Applicants will amend inventorship, if necessary, once claims are allowed. .

In summary, the Applicants have cancelled Claims 1, 9, and 10. Claims 2, 8, 11, and 13 remain pending in this application. Claims 2 and 8 have been amended. Claim 2 has been substantially amended to comply with the restriction requirement to facilitate the prosecution of the application. Based on the comments provided above, Applicants assert that the remaining claims comply with 35 U.S.C. §§ 112, 102, and 103 and respectfully request allowance of the claims.

Respectfully submitted,

/Robert D. Titus/

Robert D. Titus
Attorney/Agent for Applicants
Registration No. 40,206
Phone: 317-277-3729

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288

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